Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Benzene, [2-[(2-methyl-1-undecen-1-yl)oxy]ethyl]-

Assessment statement (CA09641)

05 April 2023

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AICIS assessment

Chemical in this assessment

Name	CAS registry number
Benzene, [2-[(2-methyl-1-undecen-1-yl)oxy]ethyl]-	2489743-82-8

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate Application Type

Health focus

Defined scope of assessment

The chemical has been assessed as:

- a fragrance component imported into Australia at up to 10 tonnes per year
- imported at up to 100% concentration for local reformulation into finished cosmetic and household products
- imported or reformulated as a component of finished cosmetic and household products at less than 1% concentration; except for the following:
    - up to 2% concentration in candles
    - up to 10% concentration in air care products – both continuous and electrical

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia and will be imported and distributed in tightly closed lacquered drums of varying sizes up to 180 kg. It will be imported either in the neat form for further local reformulation into finished cosmetic and household products or as a fragrance component in finished end use cosmetic and household products and fine fragrances at less than 1% concentration and at up to 2% concentration in candles, and at up to 10% concentration in air care products (continuous action and electrical).

Finished consumer products containing the assessed chemical at various concentrations will be packaged in containers suitable for retail sale.

Human health

Summary of health hazards

The data provided indicate that the assessed chemical is:

- likely to be of low acute oral toxicity
- not irritating to the skin and the eye
- not considered to be genotoxic
- not likely to cause systemic toxicity following repeated oral exposure (up to 1000 mg/kg bw/day in rats)
- not likely to cause adverse effects in reproductive organs, embryotoxicity or teratogenicity following repeated oral exposure (up to 300 mg/kg bw/day in rats).

Using the Defined Approach (DA) 'two out of three' in the OECD DA for skin sensitisation Guideline (No: 497), the assessed chemical is not a skin sensitiser that requires classification. However, the second key event assay of the Adverse Outcome Pathway for skin sensitisation produced positive results for skin sensitisation, and therefore, weak skin sensitisation potential of the assessed chemical cannot be ruled out completely.

No dermal or inhalation toxicity data were submitted on the assessed chemical.

Hazard classifications relevant for worker health and safety

As per the provided information, the assessed chemical does not satisfy the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017), as adopted for industrial chemicals in Australia.

Summary of health risk

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the assessed chemical through the use of a wide range of cosmetic and household products (at less than 1% concentration in cosmetics and household and fine fragrances, up to 2% concentration in candles, and up to 10% concentration in air care products). The principal route of exposure will be dermal, while ocular and inhalation exposures are also possible, particularly from air care products and from products applied by spray.

Even though the assessed chemical has not been classified as a skin sensitiser, it is noted that the assessed chemical was positive in the second key event (keratinocytes response) of the adverse outcome pathway (AOP) for skin sensitisation (see **Supporting Information**). In addition, the assessed chemical, being a profragrance, is meant to breakdown following contact with the skin or when exposed to air. While the breakdown products have also not been determined to be skin sensitisers (no test data on one of these breakdown chemicals), the OECD QSAR toolbox prediction was negative/not conclusive for the skin sensitisation endpoint for both the breakdown products and the assessed chemical.

Therefore, the skin sensitisation potential of the assessed chemical cannot be ruled out completely at higher concentrations than what is proposed to be introduced.

No acute or repeated dose inhalation toxicity data are provided on the assessed chemical. The assessed chemical is not persistent in the environment and therefore, not expected to cause inhalation risk when using at up to 10% concentration in continuous action, electrical air fresheners, that may be releasing the assessed chemical slowly in small quantities for a longer time period. Similarly, skin sensitisation effects are also not expected when the assessed chemical is used in air care products.

The repeated dose toxicity potential of the assessed chemical was estimated by calculating the margin of exposure (MOE), using the worst case exposure scenario from use of multiple products simultaneously by an individual. The total daily systemic exposure was estimated as 2.3097 mg/kg bw/day (see **Supporting information**). Using a conservative No Observed Adverse Effect Level (NOAEL) of 300 mg/kg bw/day derived from developmental toxicity on the assessed chemical in female rats, MOE of 130 was calculated. MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. It is also noted that the MOE would be 134 excluding the laundry products as these products are not applied to the skin deliberately and any accidental spillage is expected to be washed-off immediately. In addition, the MOE of 130 was derived for the worst case systemic exposure scenario considering a dermal absorption rate of 100%. The dermal absorption rate of the assessed chemical is expected to be lower than 100% due to the low water solubility (6.03×10^{-4} mg/L) of the assessed chemical.

Overall, this assessment does not identify any risks to public health that would require specific risk management measures if the assessed chemical is introduced and used in accordance with the terms of the assessment certificate.

Workers

Workers may experience exposure to the assessed chemical in its neat form during reformulation/packaging processes. As data on inhalation hazards have not been submitted by the applicant and the skin sensitisation potential of the assessed chemical cannot be ruled out completely, control measures are needed to manage the risk arising from exposure to the assessed chemical during reformulation/packaging activities.

Exposure to the assessed chemical in end use products (at less than 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons) or the use of household products in the cleaning industry.

The principal routes of exposure will be dermal and inhalation (spray products), while ocular exposure is also possible. Professionals may use personal protective equipment (PPE) to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the end use products containing the assessed chemical.

Given that risk of skin sensitisation potential of the assessed chemical cannot be ruled out completely, control measures to minimise dermal exposure are needed to manage the risk to workers (see **Means for managing risk**). Control measures to minimise inhalation exposure may be also needed if aerosols or mists are formed during the blending processes.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemical is:

- Not persistent (not P)
- Bioaccumulative (B)
- Not toxic (not T)

Environmental hazard classification

Based on the ecotoxicological information available for the assessed chemical, it is not expected to be harmful to aquatic life. Therefore, the assessed chemical does not satisfy the criteria for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) for acute and chronic aquatic toxicities (UNECE 2017).

Summary of environmental risk

The assessed chemical will be introduced as a fragrance ingredient for use in a variety of products. These uses will result in the release of the assessed chemical to sewers and to air.

The assessed chemical is readily degradable and is not persistent. The assessed chemical has potential to bioaccumulate but it is not toxic to aquatic organisms.

Although the assessed chemical is potentially bioaccumulative, it does not meet all three PBT criteria. It is unlikely to have unpredictable long-term effects and its risk may be estimated by the risk quotient method (RQ = PEC ÷ PNEC). Based on calculated RQ values < 1 for the river and ocean compartments, it is expected that the environmental risk from the introduction of the assessed chemical can be managed.

Environment

Recommendation to Department of Climate Change, Energy, the Environment and Water

The chemical may be scheduled under the *Industrial Chemicals Environmental Management (Register) Act 2021*. Information from this assessment statement will be considered as part of any scheduling process. This may include information on chemical identity, environmental hazard characteristics, GHS classification and environmental risk.

Means for managing risk

Advice to Industry

- The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during reformulation activities:
    - Use of engineering controls such as

        - Enclosed and automated processes where possible
        - Adequate workplace ventilation to avoid accumulation of vapours, mists, or aerosols

    - Use of safe work practices to
        - Avoid contact with skin
        - Avoid inhalation of mists or aerosols

    - Use of personal protective equipment (PPE)
        - Impervious gloves
        - Protective clothing
        - Respiratory protection where local ventilation may be inadequate

- A copy of the Safety Data Sheet (SDS) should be easily accessible to workers.

Conclusions

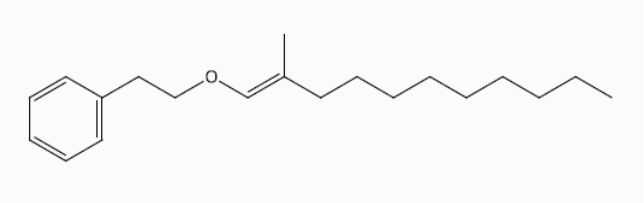
The conclusions of this assessment are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the terms of the assessment certificate the human health and environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety, and poisons legislation as adopted by the relevant state or territory, and the proposed means for managing the risks identified during this assessment are implemented.

Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	Benzene, [2-[(2-methyl-1-undecen-1-yl)oxy]ethyl]-
CAS No.	2489743-82-8
Synonyms	[2-[(2-Methyl-1-undecen-1-yl)oxy]ethyl]benzene
Structural formula	
Molecular formula	$C_{20}H_{32}O$
Molecular weight (g/mol)	288.47
SMILES	O(C=C(C)CCCCCCCCC)CCC=1C=CC=CC1
Chemical description	The assessed chemical has a degree of purity of ≥ 95%

Relevant physical and chemical properties

Physical form	Colourless liquid at 20 ºC and 101.3 kPa
Melting point	-80.4 °C
Boiling point	336.1 °C at 101.1 ± 0.2 kPa
Density	898 km/m^3 at 20 °C
Vapour pressure	4.3 × 10^{-6} kPa at 20 °C, or 8.0×10^{-6} kPa at 25 °C
Flash point	> 200 °C at 101.3 kPa
Auto-ignition temperature	255 °C at 100.9 - 101.2 kPa
Water solubility	6.03 × 10^{-4} mg/L
Ionisable in the environment?	No
pKa	N/A
log K_{ow}	8.146 at 25 °C
log K_{oc}	5.111 (calc.)

Human exposure

Workers

Reformulation

Typically, reformulation processes may incorporate blending operations that are automated or manual and may occur in a fully enclosed/contained environment, followed by manual or automated filling using sealed delivery systems into containers of various sizes. Dermal, ocular and inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemical in its neat form is possible during weighing and transfer stages, blending, quality control analysis and cleaning, and during maintenance of equipment. According to the applicant, worker exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection, impervious gloves, and appropriate respiratory protection.

Professional End Use

Exposure to the assessed chemical in end use products less than 1% concentration may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons) or the use of household products in the cleaning industry. These products, depending on their nature, could be applied in a number of ways, such as by hand, using an applicator or sprayed. The principal route of exposure will be dermal although inhalation and ocular exposures are also possible from spray products. Professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the end use products containing less than 1% of the assessed chemical.

Public

There will be widespread and repeated exposure of the public to the assessed chemical at less than 1% concentration through the use of a range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and/or inhalation exposures are also possible, particularly if the products are applied by spray or when used in air fresheners.

Data on typical use patterns of products (SCCS 2012; Cadby et al. 2002; ACI 2010; Loretz et al. 2006) in which the assessed chemical may be used are shown in the following tables. For the purposes of exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. Given the low molecular weight (288.47 g/mol) of the assessed chemical, there is potential for it to cross biological membranes, including the skin. However, the partition coefficient (log P_{ow} = 8.146 at 25 °C) implies low water solubility of the chemical to absorb through biological membranes. A worst-case dermal absorption (DA) rate of 100% was used along with a combined average body weight (BW) for males and females of 70 kg (enHealth 2012) for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling et al. 2014; Rothe et al. 2011; Earnest Jr. 2009). An adult inhalation rate of 20 m^3/day (enHealth 2012) was used and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%.

The following tables provide information on exposure estimates obtained using the above parameters.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.99	1	1.1060
Face cream	1540	0.99	1	0.2178
Hand cream	2160	0.99	1	0.3055
Fine fragrances	750	0.99	1	0.1061
Deodorant (non-spray)	1500	0.99	1	0.2121
Deodorant (spray)	1430	0.99	1	0.2212
Shampoo	10460	0.99	0.01	0.0148
Conditioner	3920	0.99	0.01	0.0055
Shower gel	18670	0.99	0.01	0.0264
Total				**2.2154**

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.99	0.95	10	0.0309
Fabric softener	90	0.99	0.95	10	0.00121
Total					**0.0430**

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.99	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	0.99	1980	0.009	0.01	0.03	0.0023
All-purpose cleaner	1	0.99	1980	1	0.01	0.007	0.0196
Total							**0.0222**

C = maximum intended concentration of assessed chemical

Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

Hair spray (inhalation exposure)

Amount of hairspray applied	9.89	g/day
Maximum intended concentration of the chemical	0.99	%
Inhalation rate of the user	20	m^3/day
Exposure duration in zone 1	1	minutes
Exposure duration in zone 2	20	minutes
Fraction inhaled by the user	50	%
Volume of zone 1	1	m^3
Volume of zone 2	10	m^3
Daily systemic exposure	**0.0291**	mg/kg bw/day

C = maximum intended concentration of assessed chemical
Total daily systemic exposure = Daily systemic exposure in zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

The worst-case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemical at the maximum intended concentrations specified in various product types. This would result in a combined internal dose of 2.3097 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% dermal absorption rate, is sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray cosmetic and household products with lower exposure.

Health hazard information

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 423), an analogue chemical was administered by oral gavage to two individual groups of female Wistar rats (3 rats/group) at 2000 mg/kg bw. All animals survived until the end of the 14-day study period. Hunched posture (6/6 female rats), uncoordinated movements (1/6 female rats) and piloerection (3/6 females) were noted between days 1 and 3. All effects fully reversed by day 4. The mean body weight gain shown by the females over the study period was considered to be normal. No macroscopic findings

were recorded at necropsy. The acute oral LD50 value for the analogue chemical was determined to be > 2000 mg/kg bw.

No acute dermal or inhalation toxicity data were submitted for the assessed chemical.

Corrosion/Irritation

Skin irritation

The assessed chemical was determined not to be irritating to skin in an *in vitro* skin irritation test using reconstructed human epidermis tissue model (EPISKIN Small mode) (OECD TG 439). The relative mean tissue viability of the test substance-treated tissues, as compared to the negative control tissues, was 111% (above the threshold for irritancy of ≤ 50%) after the 15 ± 0.5 minutes treatment period (followed by a 42-hour post-exposure incubation period). Under the conditions of the study and according to the test guideline, the assessed chemical was not considered to be irritating to the skin.

Eye irritation

The eye irritation potential of the assessed chemical was tested in a Bovine Corneal Opacity and Permeability (BCOP) test by application of 750 µL undiluted test material onto the epithelial surface of isolated bovine cornea for 10 minutes (OECD TG 437). An *in vitro* Irritancy Score (IVIS) was calculated, with an IVIS greater than 55 being indicative of risk of serious damage to eyes. The IVIS score of the test-substance was determined to be 2.4 after 10 minutes of treatment. Based on the results and as per the test guideline, the assessed chemical does not require classification for eye irritation as the IVIS score is ≤ 3.

Sensitisation

Skin sensitisation

One *in chemico* and one *in vitro* cell based assays, representing first and second key events, were conducted to evaluate the skin sensitisation potential of the assessed chemical. These tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific key events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD TG 497 (June 2021). The applicant did not submit data regarding the third key event assay, the Human Cell Line Activation test (h-CLAT) assay (OECD TG 442E).

The direct peptide reactivity assay (DPRA) is a i*n chemico* method and aims to address the first key event (KE) (molecular initiation) of the AOP by measuring the interaction of the assessed chemical with cysteine and lysine, small synthetic peptides representing the nucleophilic centres in skin proteins (OECD TG 442C). The ARE-Nrf2 luciferase assay aims to address the second key event (keratinocyte activation) of the AOP by measuring the expression of a reporter luciferase gene under the control of a promoter from the antioxidant response element (ARE), a responding gene known to be upregulated by contact sensitisers (OECD TG442D). The results of the above assays are considered using the applicable DA in the DASS Guideline for Classification and Labelling purposes.

The assessed chemical showed negative results in the first key event (molecular initiating) of the adverse outcome pathway (AOP) for skin sensitisation and positive result in the second key event (keratinocytes response) of the adverse outcome pathway (AOP) for skin sensitisation in the in Vitro Skin Sensitisation Assay (OECD TG 442d).

The skin sensitisation potential of the assessed chemical was further tested in Genomic Allergen Rapid Detection (GARD) *in vitro* skin sensitization assay for binary prediction as a sensitiser/non-sensitiser (OECD TG 442E). The test substance showed solubility limitations in cell medium when using the Standard GARD™ Assay Protocol, therefore a step dilution was used to increase the in-well concentration to the upper limit of the titration range. The assessed chemical was predicted as a non-sensitiser under the GARD assay conditions. However, due to the limitations of Gard assay, a sufficient in-well concentration of the test substance may not be guaranteed which may cause false negatives.

The applicant has also provided information on the results of the skin sensitisation endpoint prediction using quantitative structure-activity relationship (QSAR). The assessed chemical was a weak/non-sensitiser in the skin sensitisation DST Model/OASIS TIMES Prediction, non-sensitiser in skin sensitisation GHS Model/OASIS TIMES Prediction, and non-sensitiser in the skin sensitisation Autoxidation Model/OASIS TIMES Prediction. OECD QSAR toolbox prediction results for both assessed chemical and breakdown products (resulting from the auto oxidation of the assessed chemical from its use in end use products containing the assessed chemical) were negative for the skin sensitisation endpoint.

Even though the assessed chemical has not been determined to be a skin sensitiser, it is noted that the assessed chemical was positive in the second key event (keratinocytes response) of the adverse outcome pathway (AOP) for skin sensitisation. There is no explanation provided for this finding to be considered a false positive result. Based on the positive keratinocytes response in the second key event assay and a statistically derived positive QSAR prediction for an analogue chemical (using DEREK NEXUS v6.01), the applicant has classified the assessed chemical as a weak skin sensitiser (Category 1B skin sensitiser).

Repeat dose toxicity

No repeated dose dermal or inhalation toxicity data on the assessed chemical were submitted. A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) was provided (below). Under the conditions of the study, the NOAEL for repeated dose oral toxicity was regarded to be 1000 mg/kg bw/day in rats, based on no adverse effects observed at the highest tested dose (1000 mg/kg bw/day).

Genotoxicity

The assessed chemical was not mutagenic in the bacterial Reverse Mutation Assay (Ames Test) when tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA (pKM101), with or without metabolic activation (OECD TG 471). No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains at any tested dose (1.6, 5, 16, 50, 160, 500 and 5000 µg/plate), with or without metabolic activation (S9-mix).

The assessed chemical was further tested for its clastogenic and aneugenic potential in an *in vitro* mammalian micronucleus test using TK6 human lymphoblastoid cells (OECD TG 487). Three experiments were conducted: 3-hour exposure with S9-mix at 888.9 to 2000 µg/mL (experiment 1), 3-hour exposure without S9-mix at 592.6 to 2000 µg/mL (experiment 2), and 24-hour exposure without S9-mix at continuous 30.00 to 70.52 µg/mL (experiment 3). No statistically significant increases in micronucleus formation were observed at any concentration analysed. Under the conditions of this study, the assessed chemical did not induce any statistically significant increases in the frequency of cells with micronuclei, indicating that the assessed chemical was neither clastogenic nor aneugenic.

Overall, the assessed chemical is not considered to be genotoxic.

Reproductive and development toxicity

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, the assessed chemical was administered to Wistar Ham rats (10/sex/group) in corn oil via oral gavage at dose levels of 0, 100, 300 and 1000 mg/kg bw/day, once daily, 7 days a week for a minimum of 28 days (OECD TG 422).

This included a minimum of 14 days prior to mating and during the mating period. Female rats that delivered were treated for 51-63 days (same dose levels as above) - 14 days prior to mating (with the objective to cover at least two complete oestrous cycles), the variable time to conception, the duration of pregnancy and at least 13 days after delivery, up to and including the day before scheduled necropsy. Females, which failed to deliver, were treated for 37-42 days. The offspring received no direct administration of the test item; any exposure was in utero or via the milk.

Clinical Observations consisted of salivation among parental animals of the 300 and 1000 mg/kg bw/day dose groups from Day 13 of dosing onwards until the end of the treatment period. This sign was considered a physiological response rather than a sign of systemic toxicity. Even though serum levels of T4 were statistically significantly decreased in F_0-males and F_0-females at 300 and 1000 mg/kg bw/day, the mean value remained within the range of historical control data. As Thyroid Stimulating Hormone (TSH) values were considered unaffected by treatment, decreased serum levels of T4 were not considered as an adverse effect.

No test substance-related changes in body weights, body weight gain, food consumption, functional observations, motor activity, grip strength, hearing ability, pupillary reflex and static righting reflex, haematology and coagulation were observed up to 1000 mg/kg bw/day.

Higher liver weights (absolute and relative to body weight) were recorded in males at 1000 mg/kg bw/day. Additionally, higher kidney weights (absolute and relative to body weight) were also recorded in males at 300 and 1000 mg/kg bw/day. While these effects were related to the administration of the test substance, these effects were not considered adverse as these occurred without any macroscopic and microscopic correlation. Test item-related morphologic alterations were present in the kidneys of males treated at 1000 mg/kg bw/day and consisted of an increased incidence and severity in hyaline droplet accumulation. As the hyaline droplet accumulation was considered to represent alpha 2u globulin, a normal protein in male rats and is not present in man, this effect was not considered relevant to humans.

Under the conditions of the study, the NOAEL for repeated dose toxicity was determined to be 1000 mg/kg bw/day bw/day for males/females, based on no adverse effects noted at the highest tested dose (1000 mg/kg bw/day).

No toxicologically significant changes were observed in any of the reproductive parameters investigated in this study such as mating and fertility indices, precoital time, number of implantations, oestrous cycle, spermatogenic profiling, and histopathological examination of reproductive organs. Therefore, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg bw/day, based on no adverse effects noted at the highest tested dose (1000 mg/kg bw/day).

Regarding developmental effects, a lower post-implantation survival index was noted at 1000 mg/kg bw/day (93%, 91%, 92% and 78% for the control, 100, 300 and 1000 mg/kg bw/day groups, respectively). These changes could only partly be attributed to the female (# 78) at

1000 mg/kg bw/day that was sacrificed with delivery difficulties. Even if the pups of this female were born, the post-implantation index survival index would still be lower compared to the concurrent control. Therefore, a possible association of treatment with lower post-implantation survival index could not be excluded. Due to the lower post-implantation survival index, litter size was also decreased in females treated at 1000 mg/kg bw/day. No treatment-related changes were observed in any of the other developmental parameters investigated in this study such as duration of gestation, viability and lactation indices, parturition, sex ratio, maternal care, and early postnatal pup development consisting of mortality, clinical signs, body weight, anogenital distance, areola/nipple retention, T4 thyroid hormone levels, and macroscopic examination.

Therefore, based on the above effects, a NOAEL of 300 mg/kg bw/day was determined for developmental effects, based on apparent decreased post-implantation survival index observed at 1000 mg/kg bw/day.

Environmental exposure

The assessed chemical will be imported into Australia in its pure form and as a component in a fragrance formula or as a component of finished personal and household care products. Significant releases of the assessed chemical to the environment are not expected during transport or storage.

The assessed chemical is a fragrance ingredient to be included in a range of products, resulting in a variety of potential exposure scenarios.

Uses of the assessed chemical in cosmetic products, washing products and cleaning products are expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

Use of the assessed chemical in air freshener products will result in the direct release of the assessed chemical into the air compartment.

Environmental fate

Partitioning

The assessed chemical is very slightly water soluble (water solubility = 0.603 µg/L at 25°C), slightly volatile (vapour pressure = 8.0 x 10^{-3} Pa at 25°C) and has a high calculated log K_{OC} value (log K_{OC} = 5.111). When the chemical is released to water, a considerable proportion of the chemical is expected to evaporate and partition to air. The remainder of the assessed chemical is not expected to stay in water and will partition to, and be immobile in, sediments.

The assessed chemical is not expected to partition out of the air compartment when released to air.

Degradation

Based on its measured degradation in water and predicted degradation in air, the assessed chemical is not persistent.

The half-life of the assessed chemical in air is calculated to be 0.077 days (0.92 hours), based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). As its calculated half-life in air is below the domestic threshold value of 2 days, the assessed chemical is not expected to persist in the air compartment.

Degradation studies in water indicate that the assessed chemical is readily biodegradable. A supplied OECD 301F biodegradation study demonstrated 75% degradation over 28 days (according to oxygen demand). The degradation of assessed chemical with silicone oil was 93% over 28 days (according to oxygen demand). The assessed chemical satisfied the 10-day-window criterion under both conditions.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemical has potential to bioaccumulate.

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficient of the assessed chemical is log K_{OW} = 8.146, which is above the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC, 2009). This determination is considered to be conservative as the assessed chemical is not considered to be persistent.

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 100% of the introduction volume is released into sewage treatment plants (STP). This calculated value is conservative as not all uses of the assessed chemical are expected to result in release to STP. Based on its very low water solubility, slight volatility, high log Kow and ready biodegradability, a large proportion of the assessed chemical is expected to be removed by adsorption to biosolids, or through degradation and volatilisation during STP treatment. The extent to which the assessed substance is removed from the effluent in STP processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs, 1996) and is estimated to be 97%. Therefore 3% of the total introduction volume is estimated to be released to the aquatic environment. The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	10,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	27.40	kg/day
Water use	200.0	L/person/day
Population of Australia	24.386	Million
Removal within STP	97%	Mitigation
Daily effluent production	4 877	ML/day
Dilution Factor - River	1.0	

Dilution Factor - Ocean	10.0	
PEC - River	0.22	µg/L
PEC - Ocean	0.02	µg/L

These PEC values are considered to be conservative as a further portion of the calculated assessed chemical in the effluent is expected to partition to sediments, based on the log Koc value of the assessed chemical.

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Fish	96 h LC50 > 100 mg/L* mg/L	*Gobiocypris rarus* (Rare minnow) mortality and other effects OECD TG 203 Semi-static conditions Nominal concentration
Invertebrate	48 h EC50 > 100 mg/L*	*Daphnia magna* (water flea) Immobility OECD TG 202 Static conditions, closed without headspace Nominal concentration
Algae	72 h ErC50 > 100 mg/L*	*Pseudokirchneriella subcapitata* (Green algae) Growth rate OECD TG 201 Static conditions, closed without headspace Nominal concentration
Microorganisms	3 h EC50 > 1000 mg/L	Activated sludge from STPs Respiration inhibition OECD TG 209 Nominal concentration

*Test performed using only the aqueous phase of the prepared stock solutions. Nominal concentration is reported due to the very low solubility of the assessed chemical. No significant or biologically relevant effects were observed for this endpoint.

Chronic toxicity

The following measured 10th-percentile effective concentration (EC10) value for a model organism was supplied by the applicant:

Taxon	Endpoint	Method
Algae	72 h ErC10 > 100 mg/L*	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions, closed without headspace Nominal concentration

*Test performed using only the aqueous phase of the prepared stock solutions. Nominal concentration is reported due to the very low solubility of the assessed chemical. No significant or biologically relevant effects were observed for this endpoint.

Predicted no-effect concentration (PNEC)

A conservative predicted no-effect concentration (PNEC) of 1000 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the nominal endpoint value for fish, invertebrates, and algae (100 mg/L). An assessment factor of 100 was applied to this endpoint as acute toxicity data were provided for three trophic levels (EPHC 2009).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Not Persistent (Not P). Based on measured degradation under screening test conditions, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Bioaccumulative (B). Based on a measured log K_{OW} value indicating a potential to bioaccumulate, the assessed chemical is categorised as Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available ecotoxicity values above 1 mg/L, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The assessed chemical does not meet all three PBT criteria and is hence unlikely to have unpredictable long-term effects (EPHC 2009). An estimate of risk may therefore be determined using the risk quotient method.

Based on the PEC and PNEC values determined above, Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of the assessed chemical to water:

Compartment	PEC	PNEC	RQ
River	0.22 µg/L	1000 µg/L	< 0.01
Ocean	0.02 µg/L	1000 µg/L	< 0.01

For the river and ocean compartments, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the terms outlined in this assessment certificate, is not expected to pose a significant risk to the environment. As such, the risk from the assessed chemical can be managed, based on consideration of the environmental hazard characteristics and estimated releases.

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